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## **First-line temozolomide combined with bevacizumab in metastatic melanoma: a multicentre phase II trial (SAKK 50/07)**

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**Abstract:** BACKGROUND: Oral temozolomide has shown similar efficacy to dacarbazine in phase III trials with median progression-free survival (PFS) of 2.1 months. Bevacizumab has an inhibitory effect on the proliferation of melanoma and sprouting endothelial cells. We evaluated the addition of bevacizumab to temozolomide to improve efficacy in stage IV melanoma. PATIENTS AND METHODS: Previously untreated metastatic melanoma patients with Eastern Cooperative Oncology Group performance status of two or more were treated with temozolomide 150 mg/m<sup>2</sup> days 1-7 orally and bevacizumab 10 mg/kg body weight i.v. day 1 every 2 weeks until disease progression or unacceptable toxicity. The primary end point was disease stabilisation rate [complete response (CR), partial response (PR) or stable disease (SD)] at week 12 (DSR12); secondary end points were best overall response, PFS, overall survival (OS) and adverse events. RESULTS: Sixty-two patients (median age 59 years) enrolled at nine Swiss centres. DSR12 was 52% (PR: 10 patients and SD: 22 patients). Confirmed overall response rate was 16.1% (CR: 1 patient and PR: 9 patients). Median PFS and OS were 4.2 and 9.6 months. OS (12.0 versus 9.2 months;  $P = 0.014$ ) was higher in BRAF V600E wild-type patients. CONCLUSIONS: The primary end point was surpassed showing promising activity of this bevacizumab/temozolomide combination with a favourable toxicity profile. Response and OS were significantly higher in BRAF wild-type patients.

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# First-line temozolomide combined with bevacizumab in metastatic melanoma: a multicentre phase II trial (SAKK 50/07)

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**Background:** Oral temozolomide has shown similar efficacy to dacarbazine in phase III trials with median progression-free survival (PFS) of 2.1 months. Bevacizumab has an inhibitory effect on the proliferation of melanoma and sprouting endothelial cells. We evaluated the addition of bevacizumab to temozolomide to improve efficacy in stage IV melanoma.

**Patients and methods:** Previously untreated metastatic melanoma patients with Eastern Cooperative Oncology Group performance status of two or more were treated with temozolomide 150 mg/m<sup>2</sup> days 1–7 orally and bevacizumab 10 mg/kg body weight i.v. day 1 every 2 weeks until disease progression or unacceptable toxicity. The primary end point was disease stabilisation rate [complete response (CR), partial response (PR) or stable disease (SD)] at week 12 (DSR12); secondary end points were best overall response, PFS, overall survival (OS) and adverse events.

**Results:** Sixty-two patients (median age 59 years) enrolled at nine Swiss centres. DSR12 was 52% (PR: 10 patients and SD: 22 patients). Confirmed overall response rate was 16.1% (CR: 1 patient and PR: 9 patients). Median PFS and OS were 4.2 and 9.6 months. OS (12.0 versus 9.2 months;  $P = 0.014$ ) was higher in BRAF V600E wild-type patients.

**Conclusions:** The primary end point was surpassed showing promising activity of this bevacizumab/temozolomide combination with a favourable toxicity profile. Response and OS were significantly higher in BRAF wild-type patients.

**Key words:** antiangiogenic therapy, bevacizumab, first-line treatment, metastatic melanoma, temozolomide

## Introduction

Cutaneous melanoma today is considered a genetically heterogeneous disease characterised by a wide variation of genetic alterations, including the most frequent mutation in the BRAF gene [1]. This has resulted in molecular definition of melanoma subtypes [2]. Chemotherapy for metastatic melanoma remains disappointing. The median survival time is 6–9 months, depending on the bulk and location of disease at the time of tumour recurrence, and has not improved significantly in the last few decades with the currently available chemotherapy regimens. Dacarbazine, the generally accepted standard, has response rates in phase III trials of 9.8%–12% [3, 4]. Temozolomide is at least as effective in conventional dosing as it can cross the blood–brain barrier and can be given orally [3]. Two phase II trials that combined extended dose

temozolomide with thalidomide or with pegylated interferon  $\alpha 2b$  showed response rates of approximately 30% [5, 6]. In analogy to the European Organisation for Research and Treatment of Cancer 18032 study (phase III: dacarbazine versus temozolomide) [4], we decided to use the extended dosing temozolomide of 150 mg/m<sup>2</sup> days 1–7 every 14 days.

Bevacizumab is a monoclonal antibody against vascular endothelial cell growth factor (VEGF) that has shown significant survival advantage when combined with chemotherapy in advanced colorectal and non-small-cell lung cancer [7, 8]. A significant advantage in progression-free survival (PFS) was attained in advanced breast cancer [9] and non-small-cell lung cancer [10] when administering bevacizumab in combination with chemotherapy and in renal cell cancer when combined with interferon [11, 12]. Beside this, bevacizumab has the orphan drug status for glioblastoma based on a randomised phase II trial [13]. Bevacizumab recognises all isoforms of VEGF but does not recognise other peptide growth factors tested (fibroblast growth factor, epidermal growth

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factor, hepatocyte growth factor, platelet-derived growth factor and nerve growth factor). It may exert a direct antiangiogenic effect by binding and clearing VEGF from the tumour environment. Additional antitumour activity may be obtained via the effects of bevacizumab on tumour vasculature, interstitial pressure and blood vessel permeability that can lead to enhanced chemotherapy delivery to tumour cells.

VEGF receptors were found in melanocytes as well as in malignant melanoma cells and the surrounding stromal cells [14]. It could be shown in several melanoma cell lines that treatment with dacarbazine can cause higher secretion of interleukin 8 (IL8) and VEGF. Metastatic cell lines secreting high levels of IL8 and VEGF were more resistant to dacarbazine treatment [15]. Exogenously added VEGF (10 ng/ml) was able to stimulate up to 40% increased proliferation of A375 melanoma cells following a 48-h period of quiescence, suggesting that VEGF indeed plays a role in autocrine as well as paracrine stimulation of melanoma growth [16]. It was shown in human melanoma xenografts that anti-VEGF therapy inhibits melanoma growth [17]. However, tumour cells appear to express endothelial markers that do not respond to normal angiogenic control. In a recently published study, it was shown that vascular endothelial growth factor-A-driven autocrine loop promotes human melanoma cell ability to invade the extracellular matrix, which strongly supports the hypothesis that activation of vascular endothelial growth factor receptor-2 plays a primary role in this process [18]. Immunohistochemical studies have found that expression of VEGF in melanoma metastases is higher than in primary tumours and increased serum concentrations of VEGF have been found to correlate with tumour progression and survival [19]. A case series [20] as well as a few phase II studies of bevacizumab in combination with different nonstandard chemotherapy (nab-paclitaxel, paclitaxel as single agent or in combination with carboplatin) have been published so far [21–24]. One trial has combined bevacizumab with interferon  $\alpha$ 2b, and another study tested the combination with everolimus [25, 26]. The results of these trials are encouraging and warrant further evaluation of combination therapy of bevacizumab with other agents.

Considering all the points mentioned and in view of the fact that the combination of VEGF antibodies and standard chemotherapy can improve time to progression and overall survival (OS) in different tumour entities, it appeared to us a logical step to investigate the combination of chemotherapy and bevacizumab in melanoma patients as well. Because temozolomide is a standard chemotherapy regimen in metastatic melanoma, has a favourable side-effect profile and nonoverlapping toxicity with bevacizumab, we decided to test this combination in our trial. Especially, we were interested to evaluate the efficacy of this therapeutic approach in patients with BRAF-positive compared with BRAF-negative metastatic melanoma.

## patients and methods

Adult patients who had histologically confirmed stage IV metastatic melanoma; had measurable disease according to RECIST; had Eastern Cooperative Oncology Group (ECOG) performance status of two or less; had haemoglobin  $\geq 90$  g/l (may be transfused to maintain or exceed this

level), neutrophils  $\geq 1.5 \times 10^9$ /l, platelets  $\geq 100 \times 10^9$ /l, bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), alanine transaminase and alkaline phosphatase  $\leq 2.5 \times$  ULN ( $\leq 5 \times$  ULN acceptable in patients with liver metastases) and serum creatinine  $< 177$   $\mu$ mol/l and had not received prior systemic chemotherapy were included. Prior cytokine or vaccine adjuvant therapy was allowed if completed more than 4 weeks before trial registration. Prior vaccine therapy for stage IV as well as therapy of locoregional disease with perfusional therapy (limb and liver) were allowed as well. The main exclusion criteria were patients with ocular melanoma, brain metastases [magnetic resonance imaging (MRI) mandatory], uncontrolled hypertension, use of full-dose oral or parenteral anticoagulants, thrombolytic agents or use of aspirin ( $> 325$  mg/day) or clopidogrel ( $> 75$  mg/day). Major surgery within 30 days or minor surgery within 24 h before registration, serious nonhealing wound, active peptic ulcer, nonhealing bone fracture or bleeding skin metastases were also considered as exclusion criteria. Patients with history of abdominal disease, such as fistula, gastrointestinal perforation or intraabdominal abscess, not able to swallow tablets, receiving a treatment in a clinical trial within 30 days before registration, receiving concurrent treatment with other experimental drugs or other anticancer therapy, who had previous therapy with bevacizumab or other angiogenic inhibitors were not allowed to enter the trial. Pregnant or lactating women were excluded. The trial was approved by the local ethics review boards as well as by Swissmedic and was registered at the National Institute of Health ([www.clinicaltrial.gov](http://www.clinicaltrial.gov); identifier number: NCT00568048). All patients gave informed consent before any trial procedure.

## BRAF mutation status—PCR-based method

In order to determine the mutation status for the amino acid exchange at position V600E of exon 15 of the BRAF gene, quantitative real-time PCR was carried out by means of Taqman 7900HT Fast Real-Time PCR Systems (Applied Biosystems, Foster City, CA) after DNA extraction from paraffin-embedded melanoma tissue [27]. The exact method has been described elsewhere and has been used in a variety of tumour types [28].

## treatment

Participating patients received a two-drug regimen containing temozolomide 150 mg/m<sup>2</sup> on days 1–7 every 14 days orally and bevacizumab 10 mg/kg body weight i.v. over 90 min for the first infusion, 60 min for the second and 30 min for the third and subsequent infusions every 14 days. In case of grade 3 haematologic toxicity, a two-dose reduction for temozolomide was requested (dose 1: 112.5 mg/m<sup>2</sup> and dose 2: 75 mg/m<sup>2</sup>). Therapy was given until progression, unacceptable toxicity or intolerability of either of the drugs. Prophylactic antiemetic treatment with a 5-HT<sub>3</sub>-antagonist was administered before temozolomide on day 1. From day 2, prophylaxis was replaced by metoclopramide 10 mg or domperidone 10 mg. Because continued administration of temozolomide has been associated with severe lymphocytopenia with increased risk for opportunistic infections, in particular pneumocystis jirovecii pneumonia, prophylaxis with trimethoprim–sulfamethoxazole, was recommended.

## clinical assessment

Screening assessments included full physical examination and medical history, MRI of the brain, computed tomography as indicated for tumour assessment, haematology, chemistry testing and urinalysis. Physical examination, updates of the medical history, haematology (haemoglobin, neutrophils, platelets) and urine analysis were carried out before each cycle. Tumour response was assessed by investigators according to the RECIST criteria 1.0 at the end of every three cycles (i.e. every 6 weeks). Investigators were required to document all sites of disease at baseline. The longest diameter measurement of all lesions large enough to be reliably detected at baseline was summed at each tumour evaluation [i.e. sum of the longest

diameters (SLD)]. The first two tumour assessments after trial registration were reviewed by an independent blinded radiologist. The first documented partial response (PR) and complete response (CR) were confirmed by the next assessment 6 weeks later. Adverse events (AEs) were graded according to National Cancer Institute's Common Terminology Criteria of Adverse Events, version 3.0.

### statistical design and analysis

This single-arm open-label multicentre phase II trial used the Simon's optimal two-stage design with the primary end point being disease stabilisation rate at 12 weeks (DSR12) after trial registration. The trial therapy would be considered promising if the proportion of patients with disease stabilisation [CR, PR or stable disease (SD)] was 35% or more and uninteresting if 20% or less. Allowing for one interim analysis with 80% power and a 5% significance level, the total sample size comprised 62 patients. This translates into the trial therapy being considered promising if, during the final analysis, 18 or more patients experience disease stabilisation at week 12.

AEs were summarised by event type and grade over the total number of patients (worst recorded AE grade per patient).

For secondary end points, three time-to-event analyses were carried out: PFS, duration of response stabilisation (RD) and OS. PFS was defined as the time from trial registration until either a disease progression or death with patients censored at the time of starting a second-line therapy or the last time they were known to be alive without progression. RD included only patients with disease stabilisation (CR, PR or SD) and was read as the time from disease stabilisation until disease progression or death; patients were censored at the last time they were known to be alive and without disease progression if no event was observed. All time-to-event analyses were carried out using the intention-to-treat principle and estimated with the Kaplan–Meier method.

Other secondary end points included best overall response and confirmed response as well as the effect the BRAF mutation had on the primary and secondary end points. Between-group comparisons were carried out using the chi-squared test for categorical/binary end points and the log-rank test for time-to-event end points.

The data were analysed in SAS version 9.2 (SAS Institute Inc., Cary, NC).

## results

Between January 2008 and April 2009, 62 patients (40 male and 22 female) were enrolled. None of the patients were found ineligible or withdrew participation before the start of treatment. The median age at enrolment was 59 (range: 29–82) years and the median follow-up time was 20.1 (range: 1.7–32.0) months. All patients underwent at least one cycle of therapy. Further characteristics of these patients are presented in Table 1.

### disease stabilisation rate at 12 weeks

The unreviewed clinical DSR12 according to the investigators was 58% including 1 patient with a CR, 11 patients with a PR and 24 patients with SD. The independently reviewed DSR12 was 52% (10 PR and 22 SD).

### overall best response

The independently reviewed and confirmed objective response rate was 16.1% with one patient with CR and nine patients with PR. Patients with elevated lactate dehydrogenase (LDH) (28 patients) did not have a higher response rate than patients with LDH within normal range (33 patients) (6.6% versus 9.8%; *P* value: 0.4899). No correlation between experiencing hypertension and response rate

**Table 1.** Patient baseline characteristics

Characteristics	Frequency (%) ( <i>N</i> = 62)
Median age in years (range)	59 (29–84)
Sex	
Male	40 (64.5)
Female	22 (35.5)
ECOG performance status	
0	39 (62.9)
1	19 (30.7)
2	4 (6.5)
Grade of metastatic disease	
M1a	4 (6.5)
M1b	12 (19.4)
M1c	46 (74.2)
LDH before therapy	
Missing	1 (1.6)
LDH ≤ ULN	33 (53.2)
LDH > ULN, ≤ 2 × ULN	18 (29)
LDH > 2 × ULN	10 (16.1)
BRAF V600E status	
Wild type	22 (35.5)
Mutated	22 (35.5)
No amplification	18 (29.0)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

could be seen. At the end of the observation period, 1 of 32 patients with reviewed disease stabilisation at 12 weeks had not experienced progression and was censored. Median RD was 6.1 months [95% confidence interval (CI): 5.3–8.1]. Maximum percentage change in the sum longest diameter (SLD) from trial registration is depicted by a waterfall plot (Figure 1).

### PFS and OS

Median PFS was 4.2 months (95% CI: 2.7–5.4; Figure 2) and median RD was 4.4 months (95% CI: 4.1–5.7). At 6 months, 33% (95% CI: 21.7–44.8) of the patients survived without experiencing disease progression. The 6 months survival probability was 77.4% (95% CI: 64.9–86.0) and the median OS was 9.6 months (95% CI: 8.0–11.9; Figure 2). Nonstatistically significant differences in median OS was observed when stratified by LDH level: normal 11.5 months (95% CI: 8.3–13.6) versus elevated 8.8 months (95% CI: 6.5–11.8; *P* = 0.1746; Figure 3).

### toxicity

The toxicity analysis was based on all treated patients (*n* = 62). The majority of observed AEs were mild to moderate (i.e. grades 1 or 2) in severity. Thirty-two percent of all patients experienced a serious AE during the trial. The most common haematologic grade 3 and 4 AEs were thrombocytopenia (six patients, 9.7%) and neutropenia (four patients, 6.5%). Nonhaematologic grade 3 AEs were hypertension (seven patients, 11.3%), fatigue (five patients, 8.1%), haemorrhage (three patients, 4.8%), nausea (three patients, 4.8%) and vomiting (two patients, 3.2%). Other toxic effects were rare (Table 2). Of the 54 patients who died since study entry, 51 deaths were attributed to disease progression, 1 was the patient

decision, 2 are unknown and 2 deaths were attributed to the trial drugs (of these latter 2 patients one died with extensive abdominal tumour burden and bowel perforation and the other died with pulmonary infection without leuco- or lymphopenia).

### BRAF analysis

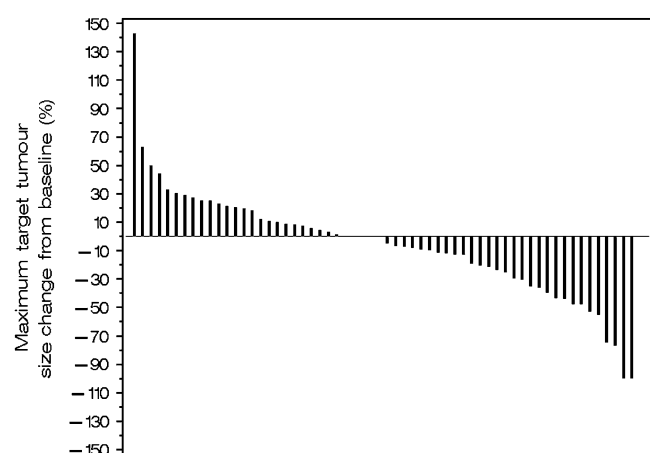
Of the 44 BRAF status results available for analysis, 22 patients had the BRAF V600E mutation and 22 were BRAF wild type. Based on the independent response review, a statistically significant association was found between BRAF status and the unconfirmed 12 weeks response favouring a response in the wild-type group ( $P = 0.0088$ ). Median PFS time in the mutated group was 4.0 (95% CI: 1.7–5.4) versus 5.4 (95% CI: 2.6–8.2) months in the wild-type group ( $P = 0.0556$ ). Median duration of disease stabilisation was 4.2 (95% CI: 3.0–5.5) versus 4.1 (95% CI: 2.7–6.9) months between the mutated ( $n = 15$ ) and wild-type ( $n = 17$ ) groups, respectively ( $P = 0.7292$ ). A statistically significant difference was found between the groups regarding OS; median OS being 9.2 months (95% CI: 6.5–11.9) in the

mutated group compared with 12.0 months (95% CI: 7.4–16.4) in the wild-type group ( $P = 0.0137$ ; Figure 4). Other prognostic biomarkers for metastatic melanoma, such as LDH, performance status and age, did not differ significantly between the BRAF mutated versus BRAF wild-type groups. Due to low numbers, no multivariable analyses are carried out regarding BRAF status.

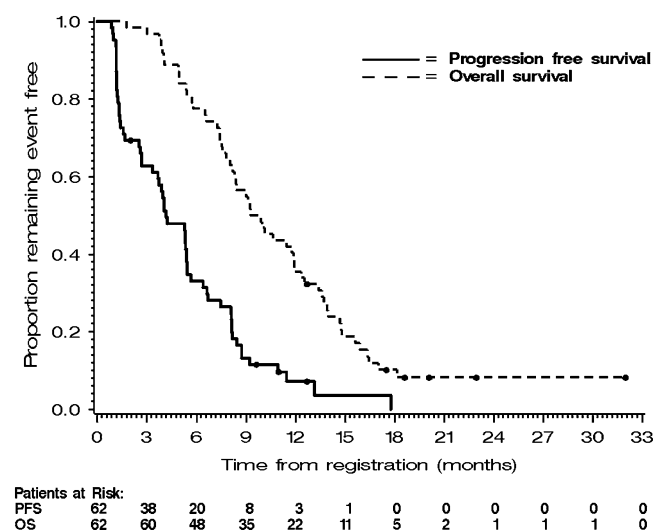
### discussion

No significant advances in the treatment of metastatic melanoma have been achieved in the last three decades. Despite several promising results in phase II trials, all phase III trials have reported negative results.

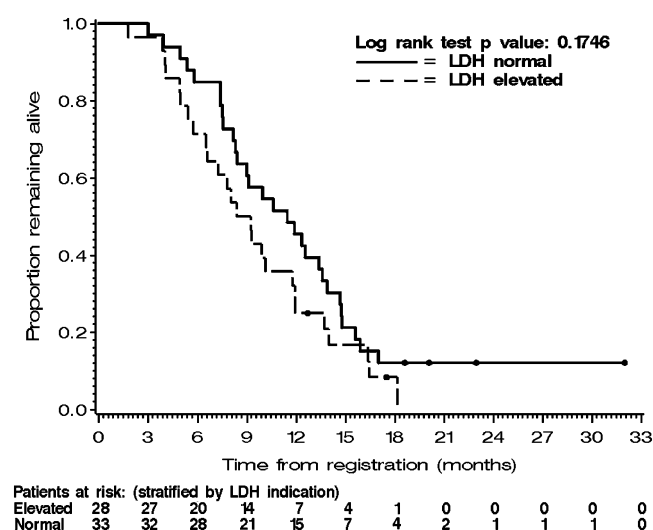
This multicentre single-arm phase II trial surpassed its primary end point of 18 or more patients with a DSR12 with an impressive 32 of 62 patients having confirmed, reviewed disease stabilisation as defined in our trial. Our response rate of 16.1% is in the same range as reported for single-agent temozolomide conventional [3] (13.5%) and extended dosing schedule [4] (14.5%), despite having studied a population at higher risk by including patients with LDH > 2 ULN (16%) and/or ECOG performance status of two (7%). The median PFS of 4.2 months compares favourably with the PFS seen in single-agent temozolomide trials (1.9–2.3 months). The median OS of temozolomide + bevacizumab was in the range of single-agent temozolomide (9.6 versus 7.7–9.1 months) [3, 4]. The extent of response rate as well as PFS is comparable to other trials that have added bevacizumab to conventional chemotherapy in melanoma patients [23, 24]. In the only randomised phase II trial of its kind, carboplatin and paclitaxel (CPP) showed a PFS of 4.2 versus 5.6 months ( $P = 0.14$ ) when adding bevacizumab (CPB) [23]. In another single-arm phase II trial with CPB dosing paclitaxel weekly, the PFS was in the same range (6.5 months) [24]. Even though the absolute numbers of PFS are slightly higher in the combination chemotherapy backbones with CPB, the extent of improvement with bevacizumab when combined with temozolomide seems to be higher compared with other chemotherapy backbone. In addition, the side-



**Figure 1.** Waterfall plot of maximal percentage change in sum of longest diameter of target tumour lesion(s) size from baseline.



**Figure 2.** Kaplan-Meier plot of progression free survival (PFS) and overall survival (OS).



**Figure 3.** Kaplan-Meier plot of overall survival stratified by normal lactate dehydrogenase (LDH) and elevated LDH.

**Table 2.** AEs (worst grade observed per patient)

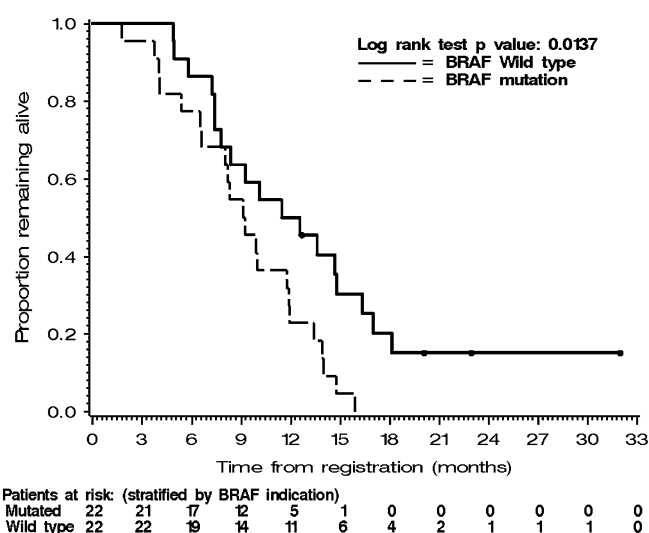
AE	CTCAE grade, n (%)		
	Grade 3	Grade 4	Grade 5
ALT	–	1 (2)	–
AST	1 (2)	–	–
Alkaline phosphatase	1 (2)	–	–
Anorexia	1 (2)	–	–
Bilirubin	1 (2)	–	–
Confusion	–	1 (2)	–
Constipation	2 (3)	–	–
Diabetes	1 (2)	–	–
Diarrhoea	1 (2)	–	–
Extensive abdominal tumour burden and bowel perforation	–	–	1 (2)
Fatigue	4 (7)	1 (2)	–
Fracture	1 (2)	–	–
GGT	1 (2)	–	–
Hand–foot syndrome	1 (2)	–	–
Haemorrhage	3 (5)	–	–
Hypertension	7 (11)	–	–
Infection with unknown ANC–NOS	1 (2)	–	–
Leucocytes	2 (3)	–	–
Lymphopenia	1 (2)	1 (2)	–
Nausea	3 (5)	–	–
Neutrophils	3 (5)	1 (2)	–
Pain	7 (11)	1 (2)	–
Platelets	4 (7)	2 (3)	–
Pulmonary infection without leuco- or lymphopenia	–	–	1 (2)
Thrombosis/thrombus/embolism	–	1 (2)	–
Trismus	1 (2)	–	–
Vomiting	2 (3)	–	–

Only grade 3 and 4 AEs are shown.

AE, adverse events; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; CTCAE, Common Terminology Criteria for Adverse Events (version 3.0); GGT, gamma glutamyl transpeptidase; NOS, disorder not otherwise specified.

effects of single-agent oral temozolomide are lower and seem to be better tolerable for the patients. In contrast to most melanoma trials, our patients with elevated LDH showed higher response rates and a statistically equal OS to the group with normal LDH value. This raises the hypothesis whether patients at high risk with rapidly progressive disease may particularly profit more from the addition of bevacizumab, which is in line with the results of the only randomised phase II trial of its kind (BEAM trial): CPP showed a PFS of 4.2 versus 5.6 months ( $P = 0.14$ ) when adding bevacizumab (CPB) [23].

Patients with a BRAF wild type had better PFS (borderline significance), OS and response rate than patients with BRAF mutation. It remains to be determined whether this mutation is only a prognostic or also a predictive biomarker. Since there are new promising targeted therapies for BRAF mutant patients such as PLX4032 in phase III trials, it appears appealing to re-evaluate these findings in BRAF wild-type patients.

**Figure 4.** Kaplan–Meier plot of overall survival stratified by BRAF wild type and BRAF mutation.

The treatment was generally well tolerated. The incidence of serious AEs in our trial was 32%, which is comparable to the 30% observed in single-agent temozolomide [4]. Bevacizumab-specific side-effects were in the range known from other trials; no new or unexpected toxic effects occurred. The good tolerability is of utmost importance in a disease where survival is mostly short and the quality of life of the remaining weeks is crucial for the patients.

In summary, the results of our trial suggest that the combination of an alkylating agent such as temozolomide with an agent that specifically targets VEGF might be a valid and interesting therapeutic strategy for patients with metastatic melanoma. A phase III trial stratifying for LDH level as well as for BRAF status is urgently warranted in a disease where no satisfactory first-line treatment exists.

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## disclosures

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## references

- Lin WM, Baker AC, Beroukhi R et al. Modeling genomic diversity and tumor dependency in malignant melanoma. *Cancer Res* 2008; 68: 664–673.
- Curtin JA, Fridlyand J, Kageshita T et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; 353: 2135–2147.
- Middleton MR, Grob JJ, Aaronson N et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol* 2000; 18: 158–166.
- Patel MP, Suci S, Mortier L et al. Extended schedule escalated dose temozolomide versus dacarbazine in stage IV malignant melanoma: final results of the randomized phase III study (EORTC 18032). *Ann Oncol* 2008 LBA 8.
- Hwu WJ, Krown SE, Menell JH et al. Phase II study of temozolomide plus thalidomide for the treatment of metastatic melanoma. *J Clin Oncol* 2003; 21: 3351–3356.
- Hwu WJ, Panageas KS, Menell JH et al. Phase II study of temozolomide plus pegylated interferon- $\alpha$ -2b for metastatic melanoma. *Cancer* 2006; 106: 2445–2451.
- Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
- Sandler A, Gray R, Perry MC et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355: 2542–2550.
- Miller KD. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. *Clin Breast Cancer* 2003; 3: 421–422.
- Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J Clin Oncol* 2009; 27: 1227–1234.
- Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon  $\alpha$ -2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; 370: 2103–2111.
- Rini BI, Halabi S, Rosenberg JE et al. Bevacizumab plus interferon  $\alpha$  compared with interferon  $\alpha$  monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 2008; 26: 5422–5428.
- Friedman HS, Prados MD, Wen PY et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009; 27(28): 4733–4740.
- Brychtova S, Bezdekova M, Brychta T et al. The role of vascular endothelial growth factors and their receptors in malignant melanomas. *Neoplasma* 2008; 55: 273–279.
- Lev DC, Onn A, Melinkova VO et al. Exposure of melanoma cells to dacarbazine results in enhanced tumor growth and metastasis in vivo. *J Clin Oncol* 2004; 22: 2092–2100.
- Liu B, Earl HM, Baban D et al. Melanoma cell lines express VEGF receptor KDR and respond to exogenously added VEGF. *Biochem Biophys Res Commun* 1995; 217: 721–727.
- Danielsen T, Rofstad EK. VEGF, bFGF and EGF in the angiogenesis of human melanoma xenografts. *Int J Cancer* 1998; 76: 836–841.
- Lacal PM, Ruffini F, Pagani E et al. An autocrine loop directed by the vascular endothelial growth factor promotes invasiveness of human melanoma cells. *Int J Oncol* 2005; 27: 1625–1632.
- Ugurel S, Rapp G, Tilgen W et al. Increased serum concentration of angiogenic factors in malignant melanoma patients correlates with tumor progression and survival. *J Clin Oncol* 2001; 19: 577–583.
- Terheyden P, Hofmann MA, Weininger M et al. Anti-vascular endothelial growth factor antibody bevacizumab in conjunction with chemotherapy in metastasising melanoma. *J Cancer Res Clin Oncol* 2007; 133: 897–901.
- Boasberg P, Cruickshank S, Hamid O et al. Nab-paclitaxel and bevacizumab as first-line therapy in patients with unresectable stage III and IV melanoma. *J Clin Oncol* 2009; 27 (Suppl): 15s (Abstr 9061).
- Gonzalez-Cao M, Viteri S, Diaz-Lagares A et al. Preliminary results of the combination of bevacizumab and weekly paclitaxel in advanced melanoma. *Oncology* 2008; 74: 12–16.
- O'Day SJ, Kim KB, Sosman JA et al. BEAM: a randomized phase II study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced melanoma. *Eur J Cancer* 2009; 7(3): 13.
- Perez DG, Suman VJ, Fitch TR et al. Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A. *Cancer* 2009; 115: 119–127.
- Varker KA, Biber JE, Kefauver C et al. A randomized phase 2 trial of bevacizumab with or without daily low-dose interferon  $\alpha$ -2b in metastatic malignant melanoma. *Ann Surg Oncol* 2007; 14: 2367–2376.
- Peyton JD, Spigel DR, Burris HA et al. Phase II trial of bevacizumab and everolimus in the treatment of patients with metastatic melanoma: preliminary results. *J Clin Oncol* 2009; 27 (Suppl): 15s (Abstr 9027).
- Newton CR, Graham A, Heptinstall LE et al. Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS). *Nucleic Acids Res* 1989; 17: 2503–2516.
- Benlloch S, Paya A, Alenda C et al. Detection of BRAF V600E mutation in colorectal cancer: comparison of automatic sequencing and real-time chemistry methodology. *J Mol Diagn* 2006; 8: 540–543.